CHAPTER

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Magnetic Resonance Contrast Media

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INTRODUCTION

Contrast in magnetic resonance imaging (MRI) is largely due to the heterogeneous distribution of tissue relaxation times, and the lack of need for contrast materials was thought to be the one major advantage of MR over other imaging techniques in the early days. Excellent soft tissue contrast, without the use of any type of contrast agent, made the procedure completely noninvasive. However, it was noted that many important pathological conditions did not show enough specific changes in their relaxation times to differentiate them from surrounding healthy tissue. Exogenous MR contrast agents were therefore developed shortly after the first commercial MR system became available in the 1980's. Presently, exogenous contrast agents are frequently used in a significant proportion of MR examinations to:

- Differentiate between similar appearing structures,
- Increase the specificity in describing regions of abnormal signal,
- Highlight or specify spaces, or
- Study the vascularity and perfusion of normal or abnormal tissues.

BASIC PRINCIPLES OF MR CONTRAST AGENTS

Contrast agents for X-ray and CT show contrasting effects according to their electron-density difference, and they produce direct contrast effects on their positions. However, the contrast mechanism is more complicated for MRI, where the contrast enhancement occurs as a result of the interaction between the contrast agents and neighboring water protons, which can be affected by many intrinsic and extrinsic factors such as proton density and MRI pulse sequences.

The basic principle of MRI is based on nuclear magnetic resonance (NMR) together with the relaxation of proton spins in a magnetic field. When the nuclei of protons, i.e the body's hydrogen atoms, are subjected to a strong magnetic field, their spins align either parallel or antiparallel to the magnetic field. During this alignment, the spins process under a specified frequency, which is known as the Larmor frequency and is dependent on the strength of the magnetic field applied. These protons absorb energy and realign from a longitudinal to a transverse axis, when a 'resonance' frequency in the radio frequency (RF) range is applied. When the RF pulse disappears, the excited nuclei return to their earlier, lower-energy state by two different relaxation pathways. The first, called the longitudinal or T1 relaxation, involves the decreased net magnetization recovering to the initial state. In the second pathway, which is called the transverse or T2 relaxation, the induced magnetization in the perpendicular plane disappears by the dephasing of spins.

MR contrast agents act by altering these relaxation times and this is measured as relaxivity. The relaxivity of a contrast agent is proportional to the magnitude of its moment, its tumbling frequency in solution and its spin relaxation time. They can be classified as T1 and T2 contrast agents, based on

their relaxation processes.

When placed in a magnetic field, molecules or ions with one or more unpaired electrons generate a magnetic moment, which aligns with the applied field. These ions or molecules are referred to as paramagnetic, superparamagnetic or ferromagnetic ions depending on their specific electronic configuration. Exogenous paramagnetic compounds of gadolinium, manganese and iron are the most commonly used MR contrast agents.

CLASSIFICATION OF MR CONTRAST AGENTS

Magnetic resonance contrast agents can be classified according to:

1. The magnetic property of the agent
2. The dominant effect of the agent on the signal intensity
3. The biodistribution of the agent.

Magnetic Properties

This is the most common method used to classify the contrast agents into 2 main groups, namely paramagnetic and superparamagnetic.

Paramagnetic Contrast Agents

Paramagnetic materials have their own magnetic field which leads to a reduction in the T1 and T2 relaxation times of the surrounding hydrogen nuclei, causing an increase in signal on T1-weighted images. There are many paramagnetic metal ions that could potentially be used as MR contrast agents but the transition metal gadolinium (Gd^{3+}) is the most commonly used ion. This is due to a favorable combination of seven unpaired electrons with a long electron spin relaxation time making it a very efficient relaxation enhancing agent. Manganese, having relaxation properties similar to gadolinium is also used. All paramagnetic contrast agents need to be chelated with an appropriate ligand to reduce the in vivo toxicity of free gadolinium or manganese.

Superparamagnetic Contrast Agents

Superparamagnetic agents also behave similarly to paramagnetic substances. Small or ultrasmall particles of supermagnetic iron oxide are used as contrast agents in clinical MRI. If the iron ions are magnetically ordered within the crystal, the net magnetic moment is so large that it greatly exceeds that of typical paramagnetic ions. This characteristic effect, of a large magnetic moment in the presence of an external magnetic field without any remnant magnetic moment when the field is zero, is called superparamagnetism. Depending on size and composition of their particles, these agents can also induce a strong enhancement of the T1-relaxation rate of water, but their dominant effect is on T2/T2* relaxation due to the large magnetic moment of the nanoparticles.

Image Enhancement

The contrast agent can either have a positive effect (increase in signal or T1-enhancement) or a negative effect (signal reduction or T2-enhancement) on the signal intensity. Mostly all MR agents affect both T1- and T2-relaxation times and the distinction relies on many MR specific parameters as well as contrast agent dose, e.g. gadolinium based contrast agents usually act as positive enhancers on T1-weighted images but also have a weak T2 negative enhancing effect whereas iron oxide based contrast agents are negative agents that have a predominant T2 and T2* shortening effect.

Biodistribution

The biodistribution of a contrast agent describes how the agent is distributed after intravenous administration.

Extracellular Fluid Agents

Small molecular weight (MW) paramagnetic agents are small enough to diffuse from the plasma into the interstitium and are thus distributed to the extracellular fluid. These agents are known as extracellular fluid (ECF) agents. They are not taken up by cells and are therefore eliminated by renal excretion with a half-life determined by the glomerular filtration rate, e.g. gadolinium based contrast agents.

Intravascular Fluid Agents

Intravascular agents are contrast agents with a MW large enough to prevent leakage from the vascular to the extravascular space. All iron oxide nanoparticles are intravascular agents, with a half-life in blood ranging from a few minutes to several hours. In blood, iron oxide agents with the appropriate

composition can produce significant T1 shortening and several studies have reported the use of nanoparticles for MR angiography. Other types of intravascular agents are based on macromolecular gadolinium compounds. Such agents are designed either by linking Gd^{3+} ions to a macromolecular polymer during synthesis or by making the Gd^{3+} complex bind to plasma proteins after injection and thus forming macromolecules in blood.

Tissue Specific Agents

Tissue specific agents are agents which have been specifically designed to accumulate in a particular organ or tissue type. Intravascular iron oxides are taken up by the Kupffer cells present in the liver, spleen and lymphatic system. Once taken up by the liver the nanoparticles will be accumulated into larger particulate clusters in the Kupffer cells and relaxation will be completely dominated by T2/T2* effects. Iron oxides can thus be said to be both intravascular agents as well as tissue specific agents. Mangafodipir trisodium and few gadolinium chelates also act as liver specific agents as they are taken up by hepatocytes.

GADOLINIUM-BASED CONTRAST AGENTS

Copper (Cu^{2+}), Manganese (Mn^{2+}) and Gadolinium (Gd^{3+}) were identified as paramagnetic ions that could shorten the T1 of water, in the early 1980s.

Gadolinium diethyle triamine penta acetic acid salt (Gd DTPA) was found to have high tolerability in animals with preserved good relaxation properties, after extensive analysis of various paramagnetic chelates. Gadolinium DTPA was first tested in humans in 1983 and the first MR contrast medium containing the pharmaceutical product Gadopentetate dimeglumine was introduced in early 1988.[1]

Gadolinium is named after the Finnish chemist Johan Gadolin.[2] Gadolinium belongs to a series of 17 chemically inert metals known as the lanthanides and has an atomic number of 64. The presence of seven unpaired electrons makes it a paramagnetic agent. The strong paramagnetic effect interferes with the relaxivity of nearby water protons and results in a reduction of both T1 and T2 relaxation times. The decrease in the T1 relaxation time is more at low concentrations of Gadolinium and this is seen as increased signal intensity on T1-weighted spin-echo or gradient-echo images.

Free Gd^{3+} ion has high toxicity in vivo as it competes with calcium. Gadolinium has a higher binding affinity for calcium binding enzymes as compared to calcium, thus it can displace calcium and alter all biological processes catalyzed by these enzymes. Free gadolinium also interacts with calcium channels to block physiological pathways that rely on calcium influx, i.e. coagulation and neural transmission.[3] Therefore, when gadolinium is chelated to an organic ligand, it is generally considered safe for use as an MR contrast agent.

Nine GBCAs have been approved for use in the United States and/or the European Union. Most GBCAs that are available are low molecular weight polyamino-carboxylate compounds **(Table 1)**.

They can broadly be classified into two categories based on their binding to serum proteins.

1. The nonspecific extracellular gadolinium chelates or agents that do not bind to serum proteins
2. The high relaxivity agents, that bind to serum proteins.

The nonspecific extracellular GBCAs include- gadopentetate, gadoterate, gadodiamide, gadoteridol, gadobutrol and gadoversetamide. These contrast agents do not bind to any protein and their biodistribution and pharmacokinetics are similar to that of iodinated water-soluble contrast media.

After intravenous injection, they rapidly diffuse into the interstitial extravascular space. There is also reverse diffusion into the intravascular compartment and an equilibrium state between diffusion in and out is usually reached within 2 hours. They are eliminated unchanged from the intravascular compartment by passive glomerular filtration and more than 95% of the injected dose is excreted in the urine by 24 hours in patients with normal renal function. A tiny amount (less than 0.1 %) is eliminated via feces. In patients with normal renal function, the biological half-life is approximately 1.5 hours.

Three basic phases of vascular and tissue enhancement occur following administration of GBCAs: arterial, blood pool and extracellular phases. Routine post contrast images are acquired when the contrast has reached the extracellular interstitial space i.e. approximately 2 minutes after injection. As the extracellular enhancement changes little over several minutes, fast scanning techniques are not essential for imaging. Interstitial enhancement is particularly conspicuous with suppression of the lipid signal intensity and T1W, fat suppressed images give the best contrast. However, if fat is nulled via inversion recovery with a short inversion time (STIR), enhancing tissue is also nulled because of its short T1 relaxation time. Therefore, the STIR technique is not advocated after administration of T1-shortening contrast agents.

Best acquisition of the arterial phase images occurs during the first pass of contrast agents through the arterial system i.e. within 20 seconds of contrast administration. Early arterial images are best for depicting arteries, and late arterial phase images are better for depicting hypervascular tissues. Blood pool or portal venous phase occurs at 60–90 seconds after contrast administration during which contrast is typically distributed throughout the body's vessels. Maximum liver parenchymal enhancement is also achieved during this phase. Dynamic imaging for detection and characterization of lesions in the liver and other organs can be performed, similar to CT, using nonspecific extracellular GBCAs.

Interstitial contrast agent is especially prominent in neoplastic tissues and areas of inflammation. Fibrous tissue has a large interstitial space and is therefore much enhanced on extracellular phase images even though it is usually hypovascular. Many metastases also have large interstitial spaces and are hyperintense on extracellular phase images. Capillaries in brain and testicular tissue are not permeable to these contrast agents, unlike capillaries throughout the rest of the body. Hence the enhancement of the brain is minimal, owing entirely to enhancement of the blood pool. Tumors and injured brain parenchyma enhance much more because of the enhancement of their interstitial space and so the depiction of brain lesions in post contrast images is very high. In addition to diffusing across tissue capillary walls, GBCAs diffuse across glomerular walls into the renal tubules, within which they are concentrated as water is reabsorbed. This makes them highly effective for enhancing the kidneys

and the urinary tract.

The high relaxivity agents include gadobenate, gadoxetate and gadofosveset. These agents bind to proteins and have a higher T1 relaxivity than the above mentioned gadolinium chelates **(see Table 1)**. Immediately after the bolus injection, gadobenate and gadoxetate, act as nonspecific extracellular gadolinium chelates but later they act as liver specific agents in the delayed phase, as they are taken up by liver cells. Excretion occurs through both, renal and hepatobiliary pathways. Gadobenate dimeglumine has a capacity for weak and transient protein binding. Approximately 2–4% of the injected dose is taken up by liver cells and its delayed imaging time is between 90–120 minutes.

TABLE 1: Gadolinium-based contrast agents approved for clinical use.[6]

Generic name	Trade name/ manufacturer	T1 relaxitivity (L/ mmol/s at 1.5 T)	Molecular weight	Excretion	Protein binding
Gadopentetate dimeglumine Gd-DTPA	Magnevist/Bayer Magnascan/ Unijules	4.1	939.0	Renal	None
Gadoterate meglumine Gd-DOTA	Dotarem/Guerbert	3.6	558.6	Renal	None
Gadodiamide Gd-DTPA-BMA	Omniscan/GE	4.3	573.6	Renal	None
Gadoteridol Gd-HP-DO3A	ProHance/Bracco	4.1	558.7	Renal	None
Gadobutrol Gd-DO3A-butrol	Gadovist/Bayer	4.7	604.7	Renal	None
Gadoversetamide Gd-DTPA-BMEA	Optimark/ Mallinckrodt	4.7	661.8	Renal	None
Gadobenate disodium Gd-BOPTA	MultiHance/ Bracco	8.3	1058.2	96% Renal, 4% Hepatic	<5%
Gadoxetate disodium Gd-EOB-DTPA	Primovist, Eovist/ Bayer	6.9	682.0	50% Renal, 50% Hepatic	<10%
Gadofosveset trisodium	Vasovist, Ablavar/ Bayer	19	958.0	91% Renal, 9% Hepatic	>85%

Gadoxetate disodium has the maximum biliary excretion (almost equal biliary and renal excretion) with a convenient delayed imaging time of 10–20 minutes. The liver parenchymal enhancement is more intense with gadoxetate as compared to gadobenate. These two agents act similar to other gadolinium chelates during the initial phase and are therefore useful in assessing tumor enhancement and characterization. They cause selective increase in the signal intensity of the liver (via hepatocyte uptake) in the later phases, thus helping in the detection of small tumors. This relies on degree of differentiation of tumors, as well differentiated hepatocellular carcinoma may take up the contrast and become less conspicuous. However, these agents are best used for detection of metastases. Also, due to the biliary excretion during the delayed phase, the biliary ducts can be mapped well using T1-weighted images.

Gadofosveset has 80–90% binding to serum albumin. This high protein binding has 2 effects: firstly it markedly increases the relaxivity (hence requiring lower doses and concentration) and secondly, it results in the agent being effectively confined to the vascular space. It has successfully been used as a blood pool agent for MR angiography, owing to its prolonged intravascular retention. The protein binding is reversible and gadofosevet is ultimately excreted unchanged by the kidneys through glomerular filtration.

As mentioned previously, it is essential to chelate gadolinium in order to reduce its toxicity. The chemical structure of chelators used to bind the gadolinium ion are different and may be linear or macrocyclic. The chemical structure of a typical linear and a typical macrocyclic GBCA are depicted in **Figures 1A and B**. Gadolinium chelates can also be categorized into 4 classes based on their biochemical structure–macrocyclic or linear, and ionicity–ionic or nonionic as given below:

Linear, ionic–gadopentetate, gadobenate, gadoxetate and gadofosveset
Linear, nonionic–gadodiamide and gadoversetamide
Macrocyclic, ionic–gadoterate
Macrocyclic nonionic–gadoteridol and gadobutrol

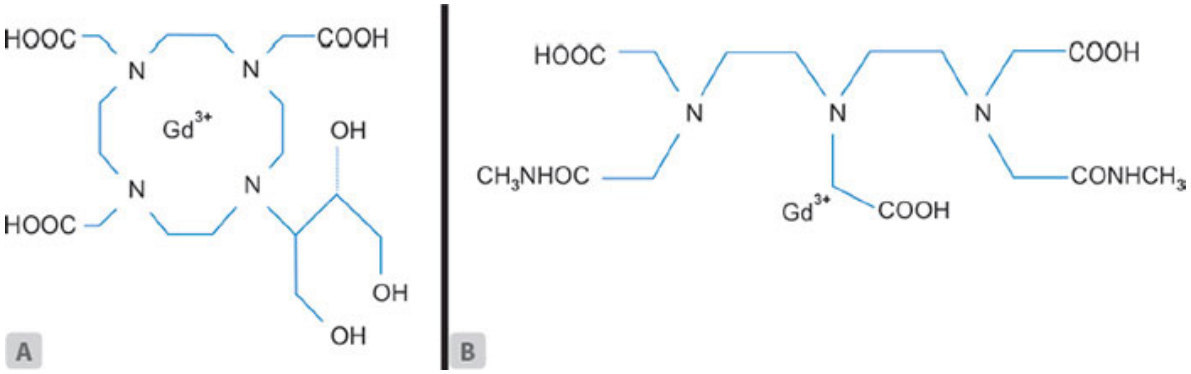
The GBCAs vary with respect to osmolality and viscosity. Their osmolality ranges between 0.63 osmol/kg to 1.97 osmol/kg **(Table 2)**. In vivo, the osmotic load of all the GBCAs is very low, compared to iodinated contrast media, as only a small amount of the contrast agent is needed to produce a diagnostic MR examination. The nonionic agents tend to have lower osmolarity and are also less viscous. Nonionic low osmolar GBCAs have lesser negative isotropic effects, which is a vital consideration for cardiac patients. Less pressure is required to inject low viscosity GBCAs and these can be administered using smaller gauge needles or catheters.

The stability of an agent describes the affinity of the gadolinium atom for its compound and is based on its thermodynamic and conditional stability. The dissociation constants **(Table 2)** can be utilized to describe the stability of the linear GBCAs. The higher the dissociation constant, greater is the stability of the agent. In contrast to the linear agents, the macrocyclic agents require a significant amount of energy to dissociate the gadolinium complexes. The kinetics of dissociation are described by the dissociation rate and the dissociation half life with these agents. In general, the ionic agents are more stable than the non-ionic agents.[4] The stability increases from nonionic linear to ionic linear to macrocyclic agents, when considering agents by class.[5,6]

Due to the toxicity of the free metal ion, many agents are bound to excess chelate **(Table 2)**. The excess chelate is considered essential because of the possibility of transmetallation with trace amounts of zinc in the blood and a consequent release of free gadolinium ion. Therefore, the least stable agents, gadodiamide and gadoversetamide, the two agents with the weakest thermodynamic stability constants, each have considerably larger amounts of excess chelate (12 mg/mL and 28.4 mg/mL respectively) as compared to the most stable agents, gadoterate and gadoteridol (0 and 0.23 mg/mL of excess chelate respectively). The presence and quantity of excess chelate can be considered as an indirect marker of the instability of the contrast agent.[6,7]

Interaction between Extracellular MRI Contrast Agents with Clinical Tests

Extracellular MRI contrast agents may cause spurious hypocalcemia as they can interfere with the assay method of calcium measurement. Knowledge of this effect on calcium measurements by some of the MRI contrast agents is essential in order to prevent incorrect and potentially hazardous treatment. It is prudent to be cautious when using colorimetric assays for angiotensin-converting enzyme, calcium, iron, magnesium, total iron binding capacity and zinc in serum samples of patients who have recently received GBCAs. Therefore, it is better to perform biochemical assays before the injection of contrast media, or delay them for at least 24 hours afterwards or longer in patients with renal impairment.



FIGS 1A AND B: Chemical structure of gadolinium-based contrast agents. (A) Typical macrocyclic agent—gadobutrol and (B) Typical linear agent—gadodiamide.

Dose of GBCAs

Generally the recommended dose for clinical use is 0.1 mmoL/kg body weight, but upto 0.3 mmoL/kg body weight may be used, particularly for MRA. Smaller doses can be used for the high relaxivity agents.

Adverse Effects of GBCAs

Extracellular MRI contrast agents are well tolerated and are associated with a low incidence of adverse effects. Mild adverse reactions such as nausea, vomiting and urticaria infrequently occur after GBCA administration. Other rare adverse effects include headache, taste disturbance, dizziness and paresthesia. While adverse reactions are infrequent in the general patient population, they are commoner in patients with a history of asthma or allergy, and in patients injected at a faster rate.[3]

These types of adverse effects are similar with all GBCAs, with no significant differences observed between various agents. The incidence of mild adverse effects is less than 5%. Anaphylactoid reactions have been reported, but they are very infrequent. Life-threatening reactions are very rare with an incidence around 1:100000. Fatal reactions may occur, however, are extremely rare.[8,9]

Contrast-induced Nephropathy

Extracellular MRI agents are more nephrotoxic than iodinated contrast media in equimolar doses. However, as the dose of gadolinium based contrast medium required for a diagnostic MRI examination is very small in comparison to doses of iodinated contrast media for CT and other radiographic examinations, nephrotoxicity due to these agents is uncommon even in patients with renal disease. In patients with marked reduction in renal function (particularly due to diabetes mellitus), contrast-induced nephropathy (CIN) may occur even at the standard doses of gadolinium based MR contrast agents.[10]

Gadolinium attenuates X-rays and hence its use for radiographic examinations instead of iodinated contrast media has been advocated in patients with history of serious adverse reactions to iodinated contrast media and in patients who are to undergo imminent thyroid treatment with radioactive iodine. In patients with renal impairment, GBCAs should not be used in place of iodinated contrast media as they can induce nephrotoxicity at the doses required to produce adequate radiographic enhancement.[3]

Extravasation

It can be challenging to monitor a patient for extravasation, particularly when the patient is deep in the bore of the MR unit. An extravasation may occur at a distance from the injection site. Extravasation of GBCAs into the surrounding tissues can result in edema, inflammation and necrosis. However, in majority of the cases the effect is minimal with no long term sequelae. Some patient categories like infants, young children, unconscious and debilitated patients, patients with arterial insufficiency or compromised venous/lymphatic drainage are less able to tolerate extravasation. Low osmolar, nonionic GBCAs reduce the risk of an extravasation as they tend to have lower viscosity, and because they are better tolerated, the severity is less following extravasation.[11]

Nephrogenic Systemic Fibrosis

Gadolinium enhanced MRI was considered one of the safest imaging procedures. However, the concern of associated nephrogenic systemic fibrosis (NSF) forced the radiology community to rethink this belief. The first case of NSF was described in 1997 as a skin disorder resembling scleromyxedema

and was termed as nephrogenic fibrosing dermopathy.[12] Later, when systemic manifestations were identified, the nomenclature was changed to nephrogenic systemic fibrosis. NSF is characterized by scleroderma—like skin changes (swelling, skin induration, skin colored erythematous papules, woody skin) that mainly affect the limbs—lower limbs more than upper limbs and trunk. Fibrotic changes may also affect other organs such as muscles, heart, lungs, oesophagus, liver, kidneys and testes. The disease can be aggressive in some patients leading to severe physical deformity or even death.

TABLE 2: Physicochemical properties of gadolinium-based contrast agents.[7]

Generic name/ trade name	Osmolality (37°C, osmol/ kg H_2O)	Viscosity (mPa at 37°C)	Thermodynamic stability constant	Conditional stability constant at pH 7.4	Metal chelates (mg/mL)	Excess chelates (mg/mL)
Gadopentetate/ Magnevist	1.96	2.9	22.1	18.1	469	0.4
Gadoterate meglumine/ Dotarem	1.35	2.0	25.8	18.8	278.3	0
Gadodiamide/ Omniscan	0.79	1.4	16.9	14.9	287	12
Gadoteridol/ Prohance	0.63	1.3	23.8	17.1	279.3	0.23
Gadobutrol/ Gadovist	1.6	4.96	21.8	14.7	605	0.5
Gadoversetamide/ Optimark	1.11	2.0	16.6	15.0	330.9	28.4
Gadobenate/ Multihance	1.97	5.3	22.6	18.4	334	0
Gadoxetate/ Primovist/Eovist	0.688	1.19	23.5	18.7	181.4	1
Gadofosveset/ Vasovist	0.825	1.8	22.1	18.9	244	0.27

The association of gadolinium with development of NSF was first described in 2006 by Grobner.[13] Since then, several studies have confirmed that gadolinium is present in the tissues of patients with NSF, thus supporting that it has a causative role in the development of this condition.[14-16] The time between the GBCA injection and onset symptoms of NSF can vary from days to months; however, in rare cases, symptoms have even appeared years after the last reported exposure.[6]

Although, the exact mechanism of NSF is not yet established, it is known to occur exclusively in patients with decreased renal function (glomerular filtration rate <30 mL/min/1.73 m^2). The most widely held hypothesis is that in patients with renal impairment there is a prolongation in the clearance time of GBCAs. This causes the gadolinium chelates to undergo transmetallation i.e the gadolinium is displaced from its chelate by other cations in the body and released in the form of free gadolinium. This free gadolinium binds with an anion such as phosphate, forming an insoluble precipitate which is deposited in various tissues leading to activation of circulating fibrocytes and subsequent fibrotic reaction in the involved tissues. The presence of gadolinium in affected tissues of NSF patients supports this theory.[15] Since the various GBCAs have varying degrees of stability in vitro and in vivo, this can help to at least partly explain why these agents differ in their apparent NSF safety profile in at-risk patients.

Currently, there is no effective treatment for NSF. Trials with corticosteroids, photopheresis, plasmapheresis, thalidomide, methotrexate, etc. have not had much success. There is also no evidence that immediate hemodialysis protects against the development of NSF. Improving renal function seems to slow or arrest progression of this condition.

Risk Factors for NSF

Patient factors: The patients at highest risk for development of NSF are those on dialysis or with acute or chronic kidney disease. It has been seen that there is a 1–7% chance of developing NSF in patients with severe chronic kidney disease (CKD4, eGFR 15–29 mL/min/1.73 m^2) and end-stage CKD (CKD5, eGFR <15 mL/min/1.73 m^2) after one or more exposures to at least some GBCAs. Only one case report of a patient with eGFR values above 30 mL/min/1.73 m^2 has been published.[17]

It has also been seen that some patients with severe CKD or acute kidney injury (AKI) develop NSF following exposure to GBCAs while others do not. In one study where 30 patients having an eGFR of under 30 mL/min/1.73 m^2 were exposed to high doses of gadodiamide (median dose of 90 mL and range of 40–200 mL), only one of the 30 patients subsequently developed NSF, an observed incidence of about 3%.[18] So it is theorized that although gadolinium is necessary for development of NSF, it is not the only trigger. A number of other possible cofactors have been postulated to play a role, including metabolic acidosis or medications that predispose patients to acidosis, increased calcium, iron, and/or phosphate levels, high-dose erythropoietin therapy, vasculopathy, immunosuppression and infection, or some other acute pro-inflammatory events.[19] As none of these have been consistently confirmed as true cofactors, routine screening for them before GBCA administration is not recommended. Hepatic disease, without the presence of AKI or severe CKD, should not considered a risk factor for NSF.[20]

Contrast medium factors: Cases of NSF have been reported for almost all GBCAs. Although it is the linear GBCAs which account for majority of NSF cases, the most commonly reported agent being gadodiamide followed by gadopentetate and gadoversetamide—NSF has also been reported for the macrocyclic formulation—gadoteridol.[21] As it is the stability of the binding of gadolinium

within the chelate which is an important factor in pathogenesis of NSF (as discussed above), the macrocyclic chelates offer better protection and binding to gadolinium ion in comparison to the linear molecules. The American College of Radiology (ACR) Manual on Contrast Media states that although the differences in the number of reported cases may be explained on the basis of the different chemical properties of various GBCAs, it could be possible that other factors like amount of market share, patient population, duration of time for which the particular agent has been in use, and a possible reporting bias may, in part, also have contributed to the differences in the number of reported cases.[20]

Based on the available data, the ACR, the European Medicines Agency (EMA) and United States Food and Drug Administration (US FDA), all have classified the GBCAs into three groups **(Table 3)**, although the scheme used by each of them is not identical. There is limited data for Group III agents, although, to date, few, if any, unconfounded cases of NSF have been reported.[20] A higher incidence of NSF is also associated with high doses of GBCAs, either as a single administration or cumulatively in multiple administrations over months to years.

TABLE 3: ACR classification of GBCAs based on reported prevalence of NSF.[20]

Group I: Agents associated with the greatest number of NSF cases
• Gadodiamide (Omniscan®) • Gadopentetate dimeglumine (Magnevist) • Gadoversetamide (OptiMARK)
Group II: Agents associated with few, if any, unconfounded cases of NSF
• Gadobenate dimeglumine (MultiHance) • Gadoteridol (ProHance) • Gadoteric acid (Dotarem) • Gadobutrol (Gadovist)
Group III: Agents for which data remains limited regarding NSF risk, but for which few, if any unconfounded cases of NSF have been reported
Gadoxetate disodium (Eovist/Primovist)

In spite of differences in the incidence of NSF, there is no evidence that any of the approved GBCAs are safe in the at-risk patient population. Conversely, in patients without renal disease, all gadolinium-based contrast agents seem to be safe. As healthcare providers have been restricting their use of GBCAs in patients at risk for NSF, the incidence of NSF has dropped drastically. This reduction reflects the changes that have been implemented in MR practice since the risks of NSF have been widely publicized.[22]

Guidelines on GBCA Usage

The ACR, the US-FDA and European Commision/European Medicines Agency (EC/EMA) have all given their recommendations on the use of GBCAs. The three groups use different words, however, there are only minor differences between their recommendations.[23] The ACR guidelines are given below:

As the risk for developing NSF varies according to the group of GBCAs being used, thus the assessment of the patients prior to contrast administration will also vary. For patients receiving *Group II agents*, in standard or lower than standard doses, the ACR committee on Drugs and Contrast Media considers that the risk of NSF is sufficiently low or possibly nonexistent such that assessment of renal function using a questionnaire or laboratory tests is optional prior to intravenous administration. Patients receiving *Group I* GBCAs should be considered at risk of developing NSF if any of the following conditions apply to the patient:

- Any form of dialysis
- Severe or end stage renal disease without dialysis
- Acute kidney injury

There is insufficient data to assess the risk of NSF after administration of *group III* agents, in spite of an alternative pathway of excretion for hepatobiliary agents. So for group I and III GBCAs renal function assessment should be done as detailed in **Table 4**.

Additionally, ACR has made recommendations for specific patient populations with compromised renal function, as given in **Table 5**.

With the recent finding of gadolinium deposition in the brain, certain additional restrictions have been imposed on the usage of GBCAs by the USFDA and EMA. These have been dealt with later in the chapter, in the section on “Gadolinium presence in brain and body”.

GBCA Administration in Children

Guidelines for intravenous use of GBCAs are generally similar in the adult and pediatric population. Only few pediatric cases of NSF have been reported and no cases have been reported in children less than 6 years of age. Nevertheless, enough data is not available to demonstrate that NSF is less likely to occur in children as compared to adults. Children who are at risk for renal impairment (e.g. chronic kidney disease or acute kidney injury) or those with renal/urinary tract structural abnormalities should be identified and screened for renal function.

TABLE 4: eGFR evaluation of renal function prior to administration of group I or group III GBCAs.[20]

Patient condition	eGFR requirement
Patient on dialysis (any type)	No eGFR required
Patient with AKI	No eGFR required
Inpatient	Obtain eGFR within 2 days of the MRI study
Outpatient/emergency with no prior eGFR at the time the MR is scheduled	If no risk factors*, no eGFR required With risk factors, obtain eGFR
Outpatient/emergency with most recent prior eGFR of 45 or above	If no risk factor and eGFR of 60 or above, no new eGFR required With risk factors and/or eGFR 45–59, if most recent prior eGFR is within 6 weeks of the MRI, no new eGFR is needed; otherwise obtain a new eGFR
Outpatient/emergency with most recent prior eGFR of 44 or below	Obtain eGFR within 2 days of the MRI study

**Risk factors*: (1) History of renal disease, including: (a) Prior dialysis, (b) Renal transplant, (c) Single kidney, (d) Kidney surgery, (e) Renal cancer; (2) Hypertension requiring medical therapy; (3) Diabetes mellitus

TABLE 5: ACR recommendations for specific groups of patients.[20]

Patient category	Recommendations
ESRD on chronic dialysis	• Consider administration of iodinated contrast media and perform CT wherever possible • If CEMRI essential—Group I agents are contraindicated, use Group II agents • Use lowest possible dose of GBCA CEMRI should be performed as closely before hemodialysis as possible
CKD 4 or 5 (eGFR <30 mL/min/1.73 m^2) not on chronic dialysis	Group I agents are contraindicated Group II agents should be used if required
CKD 3 (eGFR = 30–59 mL/min/1.73 m^2)	Development of NSF exceedingly rare in this group No special precautions required
CKD 1 or 2 (eGFR = 60–119 mL/min/1.73 m^2)	Any GBCA can be administered safely
Acute kidney injury	Group I agents should be avoided, Group II agents are preferred*

* Due to the temporal lag between eGFR and actual GFR it is not possible to determine whether a given patient has AKI based on a single eGFR determination.

The eGFR values in some premature neonates and infants may be <30 mL/min/1.73 m^2 due to immature renal function, in these children cautious use of intravenous gadolinium agents is imperative. Although not based on specific evidence, some suggest avoiding use of high risk gadolinium agents in very young children (e.g. neonates <4 weeks).[20]

GBCAs During Pregnancy and Lactation

When given in clinical doses, all gadolinium based contrast agents cross the human placenta, enter the fetal circulation and are then excreted through the kidneys into the amniotic fluid. As the fetus swallows the amniotic fluid, the excreted GBCA can be absorbed and again excreted, which raises a concern of gadolinium dissociation. There are no large well-controlled teratogenic studies of the effects of these agents in pregnant women. However, small retrospective studies of women who were exposed to gadolinium chelates during their pregnancy have not reported any harmful fetal or maternal effects.[24,25]

As it is unclear how GBCAs will affect the fetus, they should be used only with extreme caution. The ACR has recommended criteria of appropriateness in using GBCAs during pregnancy. A GBCA should only be given if the referring clinician and the radiologist feel that a) the diagnosis cannot be made without its use, and would change the management, b) delaying the examination until after delivery is not possible, and c) the required information cannot be obtained by using any other imaging modality. The above should be explained to the patient, documented in the medical records of the patient and a formal consent should be taken.[20]

If it is required to perform a contrast enhanced MRI during pregnancy, then the lowest possible dose of an agent which is believed to be at low risk for development of NSF should be used. If the pregnant patient has an impaired renal function then the same precautions should be taken as in the non pregnant patient.

Only tiny amounts of GBCAs given to a *lactating mother* reach the milk.[26] In patients with normal renal function, less than 0.04% of intravenously administered GBCA is secreted into the breast milk. Less than 1% of this oral GBCA is absorbed by the baby's gastrointestinal tract (GIT), which results in exposure of less than 0.0004% of the maternal dose to the breastfeeding baby,[27] and therefore, the ACR recommends that GBCAs can be safely administered to a lactating mother. However, the EMA recommends discontinuation of breast feeding for at least 24 hours for all patients with high NSF risk GBCAs. Ultimately, an informed decision to temporarily refrain from breast feeding should be left to the mother after communication of these facts. If the mother remains concerned about any potential side effects, she may abstain from breast feeding from the time of contrast administration for a period of 12–24 hours.

Gadolinium Presence in Brain and Body

Diposition of Gadolinium in Brain

Kanda T et al. in 2014 were the first to report an association between repeated GBCA administration and increased signal intensity on noncontrast TIW images in the dentate nucleus and globus pallidus areas of the brain.[28] Since then many clinical and experimental studies have been conducted and their findings published. Autopsy studies of brain specimens have shown gadolinium deposition in the capillary endothelium and neural interstitium of dentate nucleus and globus pallidus with a significant dose-dependent relationship.[29] The increased signal intensity has been seen to occur after

approximately five or more administrations of linear GBCAs with standard dose in patients with normal renal function and an intact blood brain barrier. Early studies did not show any increase in the signal intensity after repeated administrations of macrocyclic GBCAs.[30,31] However, some studies have reported that macrocyclic GBCAs can also cause gadolinium retention, although the exposure required was much higher for macrocyclic GBCAs than for linear GBCAs.[32] No clinical symptom or adverse health effects have been confirmed to be associated with the signal increase and/or the gadolinium deposition in the brain.

Deposition of Gadolinium in Other Organs

Besides brain, gadolinium has also been seen to be deposited in other organs like bone, skin, liver etc. A positive correlation was seen between the dose of administered GBCA and gadolinium concentration measured in bone.[33] Deposition of gadolinium in cortical bone occurs at much higher levels as compared to brain and there is a significant correlation between the two. Thus, it has been suggested that bone may serve as a surrogate to estimate the gadolinium in brain.

Regulatory Statements

In view of the uncertain clinical consequences of deposition of gadolinium in the brain and other organs, many official regulatory statements have been published to warn about the safe use of GBCAs. In 2017, the USFDA recommended that healthcare professionals should be careful when using a GBCA in patients with higher risk, such as those who may need repeated contrast enhanced MRI scans to monitor a chronic condition, children and pregnant patients. The FDA also recommended a new class-wide warning about gadolinium retention in the labeling of GBCAs; and a new patient medication guide that should be informed to the patient before receiving a GBCA.

The EMA has placed restrictions on using linear gadolinium agents in the Eurpopean union from November 2017. It has recommended:

- Suspension of all multipurpose intravenous linear agents (gadoversetamide, gadopentetic acid, and gadodiamide)
- Intravenous linear agents such as gadobenic acid and gadoxetic acid to be used only for liver scans when they meet an important diagnostic need
- Gadopentetic acid only to be used in intra-articular applications, as the gadolinium concentration in the formulation used for joint injections is very low.
- Macrocyclic agents (gadoteric acid, gadobutrol, and gadoteridol) can continue to be used in their current indications but at the lowest doses that enhance images sufficiently and only when unenhanced body scans are not appropriate.

Gadolinium Deposition Disease

In 2016, Semelka et al. proposed this name for a disease process observed in subjects with normal or near normal renal function who develop persistent symptoms that arise hours to 2 months after the administration of GBCAs.[34] These symptoms may include pain in the lower arms and legs, persistent headache, bone and joint pains, clouded mentation, subcutaneous soft tissue thickening and excruciating pain. In these cases, no pre-existent disease or subsequently developed disease of an alternate known process was present to account for the symptoms. The authors believe that although this is an uncommon entity, radiologists and physicians should be aware of it and not ignore severe symptoms after administration of GBCAs.[35]

MANGANESE-BASED CONTRAST AGENTS

Manganese (Mn^{2+}) like gadolinium (Gd^{3+}) is also a strongly paramagnetic substance as it has five unpaired electrons in its structure. Its compound, Mangafodipir trisodium (MnDPDP, Teslascan) is chemically similar to vitamin B_6, and so it is specifically taken up by hepatocytes. As it causes an increase in the signal intensity of normal hepatic parenchyma it gives a high lesion-to-liver contrast. Thus it improves detection and characterization of liver lesions.[36] In the later phases, MnDPDP is excreted through bile leading to excellent biliary ductal detail and helping in the diagnosis of various biliary pathologies.[37] MnDPDP was also found to collect in the pancreatic parenchyma and so has been clinically useful for the evaluation of pancreatic lesions.

Unlike the GBCAs, MnDPDP readily dissociates to yield free manganese ions after injection. The instability of the chelate raised concerns about potential toxicity. In chronic exposure, free manganese, can accumulate in the brain and cause a parkinsonism-like syndrome. It can also have a depressive action on heart function. Moreover, in patients with chronic liver failure whose ability to excrete manganese is reduced, significant neurological risk maybe associated with manganese intoxication. Hence, MnDPDP has effectively been withdrawn from the market.[7]

Mn-based nanoparticles are currently under research for use as high performance contrast agents with reduced toxicity.

IRON OXIDE-BASED CONTRAST AGENTS

Superparamagnetic iron oxide particles were suggested as potential liver specific MR contrast agents as early as 1980s. These agents contain a crystalline core of water insoluble iron oxide crystals, usually magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3) with a core diameter between 4–10 nm. These iron oxide crystals are coated by dextran or some other biodegradable polysachharide which prevents particle aggregation and makes the total size of the iron oxide particle substantially larger and also modifies their biological behavior.[38]

Each iron oxide crystal contains several thousand paramagnetic ions (Fe^{2+} and Fe^{3+}). When subjected to an external magnetic field, these particles exhibit strong magnetization which causes microscopic field inhomogeneity and activates the dephasing of protons. Thus, iron oxide nanoparticles shorten T2 and T2* relaxation times of the neighboring regions, and lead to a decrease in signal intensity in T2- and T2* weighted MR images.

Unlike low-molecular weight water soluble GBCAs, iron oxide agents do not leak into the interstitium and therefore, behave as intravascular contrast agents as long as the endothelium of the vessel wall

is not altered by any pathological process. They are excreted from the blood by the reticuloendothelial system (RES) cells in liver, spleen, lymph nodes and bone marrow.[38]

The blood half-life and biological distribution of the nanoparticles is directly dependent on their size. They have been subdivided into two groups based on their mean total diameter and the distribution of particle sizes of the iron oxide agent (1) Superparamagnetic iron oxide particles (SPIOs) (2) Ultrasmall superparamagnetic iron oxide particles (USPIOs).

1. *Superparamagnetic iron oxide particles (SPIOs):* These are particles with aggregated iron oxide cores and a mean particle diameter greater than 50 nm. Two SPIOs have been approved for MR imaging:
   a. *Fexumoxide* (also known as Feridex or AMI-25) has a particle size of 50–180 nm, with a thin, incomplete dextran coating that makes individual particles form polycrystalline aggregates. These aggregates behave as large particles in solutions or within cells. They are eliminated quickly by reticuloendothelial cells and are cleared from the blood in less than an hour. Ferumoxide is administered as a slow intravenous infusion over 30-60 minutes and imaging performed 1–4 hours after the infusion. The liver appears darkest in the first 24 hours after the infusion, on T2* weighted and T2-weighted images. Complete metabolism needs 14–28 days but typically, the signal intensity of the liver returns to normal within 7–14 days. The most common complication of Feridex is acute severe low back pain, which may lead to discontinuation of the infusion in patients. This complication can be minimized with a slow infusion.[39]
   b. *Ferucarbotran* (also known as Resovist or SH U 555 A). This has a particle size of about 60 nm and the particles are coated with low molecular weight carboxydextran. Resovist is available as a ready to use formulation. It is administered as a rapid bolus and so can be used with both dynamic and delayed imaging. The most common adverse events with Resovit are vasodilation and parasthesias with an overall reported incidence of 7.1%.[7]
   As mentioned before, these iron oxide contrast agents are phagocytosed by macrophages within the body and so these agents are entrapped by the Kupffer cells in liver and spleen, leading to a reduction in the T2 relaxation time of these organs. Thus the normal liver appears dark on T2-weighted images. As most liver tumors, whether malignant or benign, are deficient in Kupffer cells, they do not take up SPIOs and appear relatively hyperintense after SPIO administration. However, tumors which are well differentiated and have not lost all their Kupffer cells, will take up SPIO agents and exhibit a reduction in signal intensity.[37,39] Some, not all, focal nodular hyperplasias show SPIO uptake. SPIO agents may also help to improve detection of HCC in cirrhotic patients. SPIO agents may also be used in combination with GBCAs to increase overall lesion detection.[39]

2. *Ultrasmall superparamagnetic iron oxide particles (USPIOs):* These are particles with non-aggregated (monodisperse) iron oxide cores with mean diameter less than 50 nm. As USPIOs are very small, they are extravasated from the blood vessels into interstitial spaces and transported to lymph nodes via the lymphatic channels. MR imaging is done 24–36 hours after contrast administration. The accumulation of the contrast within the normal nodes causes them to appear dark in T2 or T2* weighted while diseased nodes (e.g. metastatic nodes) do not show any change in signal intensity and appear uniformly or focally bright. When the hyperintense focus accounts for more than 30% of the nodal area, the node is considered metastatic. Harisinghani et al reported the successful detection of lymph-node metastases in patients with prostate cancer using USPIOs.[40] Sinerem and Combidex are two commercially available USPIO agents. USPIOs have also been tested as blood pool agents as they remain in the intravascular space for a long time.[41]

ORAL CONTRAST AGENTS

Oral contrast agents are required to: (1) delineate bowel pathology, and (2) distinguish bowel from other organs or mass lesions. An ideal oral contrast agent should have the following properties: (i) no or minimum absorption in the gastrointestinal tract, (ii) be completely excreted, (iii) should not lead to any motion or susceptibility artifacts, (iv) homogenous distribution within the GI tract, (v) good acceptance by the patient in terms of taste, amount of volume to be ingested and timing of administration, (vi) be safe and (vii) cost effective. A number of oral contrast agents have been developed to improve demarcation of the bowel in MR imaging studies. Broadly they can be classified as:

- Low-low intensity agents (proton displacement or T2 shortening) which have low signal intensity on all pulse sequences
- High-high intensity agents (T1 shortening) which have high signal intensity on all pulse sequences
- Low-high intensity agents (water based) have a low signal intensity on T1-weighted images and high signal intensity on T2-weighted images and
- High-low intensity agents (T1 and T2 shortening) which give a high signal intensity on T1-weighted images and low signal intensity on T2-weighted images

The last two categories are also known as biphasic agents.

Low-low Intensity (Dark Lumen) Agents

The signal intensity in bowel can be reduced by displacing the bowel contents with a material that contains no protons, such as air. Air can be administered by intubating the small bowel or rectum. However, due to patient discomfort and degradation of T2* weighted gradient echo images and echoplanar images by susceptibility artefacts, air is not featured as an oral contrast agent.

Perfluorocarbons are agents which do not contain protons, but they have the same susceptibility as water and thus, do not cause artefacts. Perflubron, a perfluorocarbon formulation was the first oral MR contrast agent approved for clinical use. However, as it was very expensive, it was withdrawn from the market.

SPIOs in high concentration can shorten T2 and T2* enough to eliminate signal from bowel even on so-called T1-weighted images. Their major disadvantage is the resulting distortion of the local magnetic field, which can exacerbate artefacts making fat-suppression particularly vulnerable. Ferumoxsil—a silicone-coated SPIO is commercially available as GastroMARK (Mallinckrodt) or Lumirem (Guerbert)

for use as an oral contrast agent. Side effects such as nausea and vomiting, flatulence and feeling of fullness were reported in 15% of patients.[42]

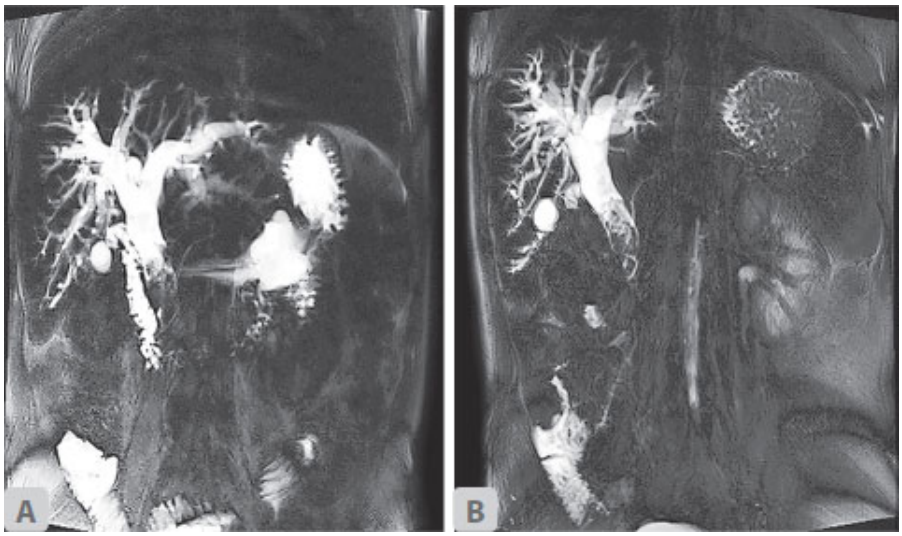
Pineapple juice also shortens T2 relaxation time and hence leads to decreased T2 signal intensity on a standard magnetic resonance cholangiopancreatography (MRCP) sequence just like the commercially available negative contrast agent—Ferumoxsil due to its high manganese content (92.76 gm/dL).[43] Oral administration of 44 mL of pineapple juice, 15 minutes before acquiring MRCP sequence, gives a significant improvement in visualization of the pancreaticobiliary channels, due to suppression of the high signal intensity (SI) in the overlapping stomach and duodenum **(Figs. 2A and B)**.

Clays such as kaolin, attapulgite and helonite restrict the motion of water, thus shortening the T1 and T2 relaxation times. However, T1-weighted gradient echo images with a TE of less than 3 msec have little T2 contrast and therefore depict clay in bowel contents as high signal intensity owing to their short T1.[44]

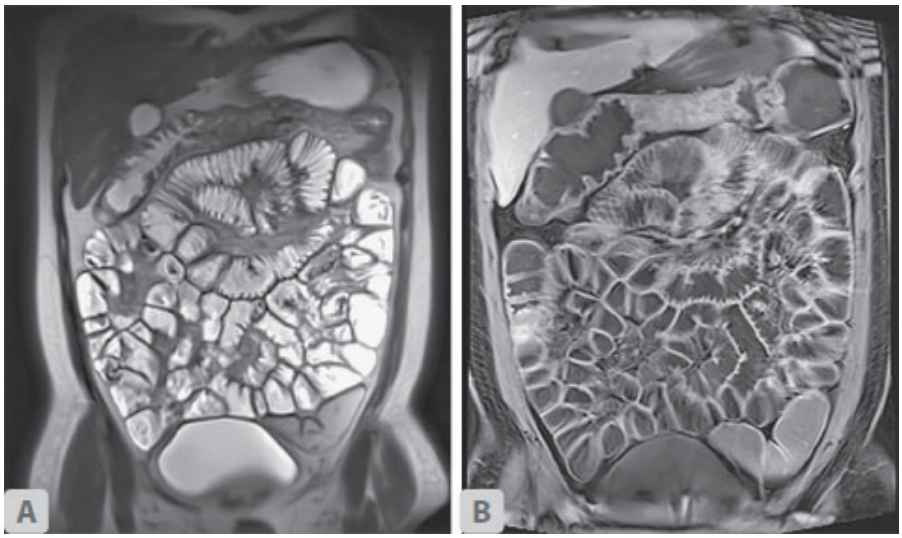
High-high Intensity (Bright Lumen) Agents

Positive contrast agents reduce the T1 relaxation time; thus they act on T1-weighted images causing an increase in the signal intensity of bowel lumen (bright lumen). Paramagnetic materials, mainly gadolinium chelate solutions but also ferrous and manganese ions are examples of positive contrast agents. Gadolinium chelate solution was one of the first contrast agents proposed as an oral contrast for MRI. Dissolved in water at a concentration of approximately 1 mmol/L, gadolinium chelate provides sufficient reduction of the T1 relaxation time of water to generate an increase in signal intensity on T1-weighted images. Due to its low concentration, it has no T2 effect, and does not shorten the T2 relaxation time; consequently the signal intensity is high even on T2-weighted images. Gadopentetate dimeglumine solution (Magnevist Enteral) was one of the first commercially available positive oral contrasts.

Blueberry juice can be used as a positive agent due to its high content of manganese, a paramagnetic ion, which shortens the T1 relaxation time. Fat containing food materials like vegetable oils, milk and ice cream also provide a high signal on T1-weighted images as they have an intrinsically short T1.[42]



FIGS 2A AND B: T2 Half Fourier acquisition single shot-turbo spin echo (HASTE) thick slab coronal MRCP image (A) in a 60-year-old male patient shows dilatation of upper common bile duct (CBD) and intrahepatic biliary channels. Fluid filled duodenum overlaps the distal CBD. (B) T2 HASTE Thick slab coronal MRCP image in the same patient after oral ingestion of 400 mL pineapple juice shows suppression of fluid signal from duodenum and stomach. The distal CBD is now better visualized and shows a filling defect within due to calculus. Pineapple juice acts as a negative oral contrast suppressing the high signal due to fluid in upper GIT.



FIGS 3A AND B: Biphasic agents—low-high intensity. T2W coronal image (A) shows good distension of the small bowel, with high intraluminal signal intensity (positive effect) and hypointense bowel wall (B) On T1 fat suppressed (FS) coronal image, after administration of intravenous gadolinium, the bowel appears hypointense with enhancement of its wall by the intravenous gadolinium, allowing excellent depiction of bowel wall.

High-low Intensity Agents

These agents shorten both T1 and T2 relaxation times in such a way that the bowel contents have high signal intensity on T1-weighted images and low signal intensity on T2-weighted images. The main advantage is that the resulting signal intensity of bowel on all the pulse sequences is different from that of tumors and simple fluid collections, which tend to have low signal intensity on T1-weighted and high signal intensity on T2-weighted images. However, some T2-weighted pulse segments (e.g. fast spin echo) may depict bowel more clearly if its contents have high signal intensity, so this form of contrast is not necessarily desirable for every application.

Examples of this type of contrast agent include clay, gadolinium chelates in high concentration and compounds of manganese. Manganese is present in high concentrations in some foods such as bananas and blueberries.

Low-high Intensity Agents

The least expensive, most widely available, and best understood oral contrast agent used for MRI is water, which causes bowel to be low signal intensity on T1-weighted and high signal intensity on T2-weighted images. It provides good small bowel distension, but its main limitation is that it gets absorbed in the intestine, which leads to poor distention of the distal small bowel. For this reason, certain substances are added to the water which reduce intestinal absorbtion e.g. mannitol, sorbitrate, etc. **(Figs. 3A and B)**

Dilute suspension of barium sulphate or dilute solutions of iodinated contrast material such as those used in opacification of bowel for CT are also very useful as low-high MR oral contrast agents.

Polyethylene glycol (PEG) is a strong hydrophilic molecule, which has the added advantage of nonabsorbability. With oral administration of 600 mL of PEG, a good distension of bowel loops can be acquired, and there are no significant side effects.[42] Low-high agents are also useful for delineating the pancreas.

However, the disadvantage of these agents is that bowel may be difficult to distinguish from simple fluid collections and tumors. High bowel signal intensity can also intensify motion artefacts.

The choice of a single agent has both, advantages and disadvantages, and so the radiologist has to choose the appropriate contrast agent according to clinical setting, availability of agent, patient tolerance and experience.

ONGOING RESEARCH AND FUTURE TRENDS

Currently most MR contrast agents are useful in improving visibility and definition of pathology, but are not suitable for extended intravascular (blood pool) or tissue/organ specific imaging and do not allow molecular imaging. There have been continuing efforts in searching for more specific contrast agents that can offer diagnosis with the accuracy approaching that otherwise only achievable with biopsy or histopathology. T1 nanoparticulate agents, target specific agents—capable of targeting organs, sites of inflammation and specific tumors, smart agents like enzyme activated agents, chemical exchange saturation transfer (CEST and PARACEST) agents, fluorinated agents, are some of the agents under research. A gadolinium free contrast agent, in view of its deposition in the body, a zwitterion coated exceedingly small superparamagnetic iron oxide nanoparticles (ZES-SPIONs) is also being developed. The majority of these agents are in pre-clinical levels of research; however, successful in vivo imaging has been reported with many pre-clinical studies. [41,45-48]

CONCLUSION

At present gadolinium chelates are the most widely used contrast agents in MR imaging and the only MR contrast agents available in India. They are easily available, have good tolerability and provide excellent lesion detection and characterization. The main concern with GBCAs was NSF, which was seen to occur only in patients with severe renal disease. Since the risks of NSF have been widely publicized leading to a change in MR practice, there has been a marked reduction in the incidence of NSF. Currently, the uncertain long term clinical consequences of gadolinium deposition in the brain, has precipitated restrictions in the use of linear GBCAs. The tissue-specific agents can be used for specific indications, depending on their availability.

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